REMARKS

Status of the claims

Prior to this amendment, claims 2 - 10 and 12 - 41 were pending. Claims 42-45 are new. Support for "elastase inhibitory activity of AAT and domains thereof, and the tryptase inhibitory activity of SLPI and domains thereof as well as for the recitation of the language "domain", may be found throughout the specification, including the drawings, and for example, at paragraphs [0061], [0063] and [0094]. Support for the recitation in claims 43-45 of protease inhibitory activities possessed by AAT, SLPI and fusion thereof, may be found throughout the specification and particularly in paragraphs [0063], [0067], [0068], [0094], [0124], [0159], [0160], [0161], [0162], [0174], [0180, and [0202].

Claims 3, 5 - 7, 9, 10, 12 - 15, 18 - 35 and 38 - 41 have been withdrawn from consideration as drawn to non-elected subject matter, with method claims 26 - 35 and 38 - 41 to be considered for rejoinder at such time as allowable composition claims are identified.

Claims 2, 4, 8, 16, 17, 36 and 37 have been examined.

Claims 2 and 8 are rejected. Claims 4, 16, 17, 36 and 37 are allowable if rewritten in independent form to include limitations from all claims from which they respectively depend.

Rejections under 35 U.S.C. §103

Claims 1 and 8 are rejected under 35 U.S.C. § 103 as being obvious over AU-B-13288/88 (the "Australian patent"), further in view of Bingle *et al.*, *Thorax* 51:1273 - 1274 ("Bingle"). Applicants respectfully traverse.

As noted previously, the Australian patent describes the cloning and gene structure of hLS2. In addition, the Australian patent describes exon swapping of hSL2. However, there is no teaching or suggestion of purely chimeric fusion forming multi-functional protease inhibitors that contain intact protease ihibitor components.

Also, as described before, Bingle suggests that "[i]nhaled recombinant SLPI (rSLPI) could prove beneficial in partnership with α1-PI in the treatment of a number of inflammatory lung disorders. . . . " "rSLPI has been successfully administered to patients with

cystic fibrosis. . . . It is feasible that rSLPI could be used to treat other inflammatory lung disorders which involve NE [neutrophil elastase] including emphysema, bronchiectasis, pulmonary fibrosis, acute lung injury and bronchopulmonary dysplasia. Probably the most effective treatment would entail combining SLPI and α1-PI. . . . ". However, it is agreed that Bingle neither teaches nor suggests fusing SLPI to AAT to create the singular molecular entity fusion proteins of Applicants' claims 2 and 8.

In contrast, the present claims are directed to a fusion protein having alpha 1-antitrypsin or a functionally active portion thereof and secretory leukosyte protease inhibitor or a functionally active portion thereof, wherein said fusion protein has alpha 1-antitrypsin protease inhibitor activity and secretory leukocyte protease inhibitor activity. In other words,the claims are directed to a fusion protein having two distinct protease inhibitory activities. Both of the activities are found in a single fusion protein and are derived from the protease inhibitor activity of the respective individual protease inhibitors.

As the Examiner is aware there are three requirements to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); M.P.E.P. § 2142; *Cf. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999) (Declaring that the level of ordinary skill in the art cannot be relied upon to provide the suggestion to combine references). Moreover, the prior art must suggest the specific modification that is necessary in order to arrive at the claimed invention. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 934, 15 U.S.P.Q.2d 1321, 1323 (Fed. Cir. 1990), cert. denied, 498 U.S. 920 (1990) ("It is insufficient that the prior art disclosed the components of the patented device, either separately or in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor."); *See also Ex parte Dussaud*, 7 U.S.P.Q.2d 1818, 1820 (Bd. Pat. App. & Int'f 1988) ("The mere fact that the prior art could be modified in the manner proposed by the examiner would not have made the modification obvious unless the prior art suggested the desirability of the modification.").

Second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q. 1016, 1023 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991); *In re Erlich*, 22 U.S.P.Q. 1463, 1466 (Bd. Pat. App. & Int. 1992); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 ("Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure."). Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness.

And third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2142.

Here, Applicants submit that the prior art references alone or in combination fail to provide adequate motivation for the combination of the references. First, as noted previously, neither of the individual references, nor the combination of references teaches or suggests creating a fusion protein having two distinct protease inhibitor activities. The Australian patent mentions that the invention "provides an approach to the preparation of bifunctional proteins which, for example, contain the activities of angiotensin II and antitrypsin" (see p. 5, lines 26-28). However, as noted before, angiotensin II is an 8 amino acid peptide that the authors only refer to in making this suggestion. There is no evidence that such a fusion was actually created or would have been effective. Also, Applicants note that angiotensin II is not a protease inhibitor. In fact, the only way to produce a fusion protein containing angiotensin II and antitrypsin, according to the method disclosed in the Australian patent, is to combine the exon-swapped hybrids from HSL-2 and either or both of rat angiotensinogen and human AAT and this will result in the angiotensin II-and antitrypsin hybrid only if angiotensinogen is *cleaved* in two successive protease cleavage steps.

Thus, the suggestion in the Australian patent relies on *cleavage* to produce one of the molecules in the briefly suggested fusion (that itself does not include a fusion protein with bifunctional protease inhibitor activity). This is in stark contrast to the presently claimed invention which is directed to bi-functional protease inhibitors- not protease substrates.

Accordingly, Applicants submit that the Australian patent teaches away from the creation of a bifunctional protease inhibitor inasmuch as it would require cleavage of protease substrates to create a fusion protein that itself is not a bifunctional protease inhibitor.

The Examiner appears to rely on the statement in Bingle that SLPI and AAT are the most effective for treatment of diseases such as inflammatory lung disorders....when used in combination (see p. 3 of the office action). However, Applicants submit that this treatment in combination in no way suggests a fusion protein. As noted previously, applicants respectfully submit that the qualified and conditional nature of Bingle's actual language -- "***could prove*** beneficial", "***feasible that*** rSLPI ***could be used***", and "***[p]robably*** the most effective ***would*** entail" fails to provide motivation to combine the teachings of Bingle with the teachings of the Australian patent to generate a fusion protein as claimed. At best, Bingle hypothesizes that co-administration of the two separate molecules could be beneficial.

As noted previously, there are convincing reasons in Bingle that teach away from such a fusion. Namely, fusion obligates the administration of the two agents in fixed, typically 1:1, stoichiometry, on a common dosage schedule, by common route of administration, in common formulation. Nothing in Bingle suggests the desirability of so constraining the clinical administration of these two agents. In addition, Bingle's comment that SLPI remains potent when oxidized, in contrast to AAT, would suggest that SLPI be less frequently administered, or in lower dosage, than AAT, teaching away from their fusion. Thus, Bingle teaches away from a combination with the Australian patent because the dose of each protease inhibitor will likely need to be independently adjusted, a variable negated by the generation of a fusion protein. As such, not only is there no teaching or suggestion in the art to combine the references, Applicants submit that one of skill in the art would be led away from combining the teachings in light of the differential doses that Bingle alludes to.

Applicants respectfully submit that the cited art neither provided the motivation to make applicants' invention, nor a reasonable expectation of successfully so doing. The Examiner's *prima facie* case of obviousness is thus unfounded, *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of

the prior art."), the burden of production has not properly been shifted to applicants, and applicants are entitled, without more, to their claims, *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992).

CONCLUSION

Applicants submit that the present claims are in condition for allowance, and respectfully request that withdrawn method claims be rejoined and examined. If the Examiner believes that any matters remain outstanding, however, applicants respectfully invite the Examiner to call the undersigned to schedule a telephonic interview.

Respectfully submitted,

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